Calcified Tissue International (2019) 104:262–272
https://doi.org/10.1007/s00223-018-0498-x

ORIGINAL RESEARCH

# Fracture Risk in Women with Dysglycaemia: Assessing Effects of Baseline and Time-Varying Risk Factors

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Received: 21 September 2018 / Accepted: 22 November 2018 / Published online: 27 November 2018


## Abstract

Although individuals with diabetes appear to have a higher fracture risk compared to those without diabetes, fracture risk in impaired fasting glucose (IFG) has not been thoroughly explored. This study determined associations between glycaemia status and fracture risk. Women ($n=575$, aged 50 + years) enrolled in the Geelong Osteoporosis Study, were followed from baseline (1993–1997), to date of first fracture, death or December 31, 2010, whichever occurred first (median 13.7 years, IQR 7.4–14.8). Hazard ratios (HRs) for any fracture (excluding fingers, toes, skull/face), as well as major osteoporotic fracture (MOF, clinical spine, hip, proximal humerus, wrist), in diabetes ($n=69$), IFG ($n=250$) and normoglycaemia ($n=256$), were calculated using a Cox proportional hazards model. Normoglycaemia was set as the reference category. A Cox proportional hazards model with time-varying covariates was also used to assess change in baseline risk factors at the 10-year follow-up visit (2004–2008). During follow-up (6433 person-years), 162 women sustained any fracture and 104 had a MOF. Unadjusted fracture risk was higher in diabetes (HR 1.64; 95% CI 1.02–2.63) compared to normoglycaemia, but IFG and normoglycaemia had similar risk (HR 1.06; 95% CI 0.76–1.47). Age- and BMD-adjusted any-fracture risk in diabetes compared to normoglycaemia was greater (HR 1.59; 95% CI 0.98–2.58); IFG was similar to normoglycaemia (HR 1.01; 95% CI 0.72–1.41). For MOF, unadjusted and age- and BMD-adjusted fracture risk in IFG was similar to normoglycaemia HR 1.02; 95% CI 0.74–1.40 and HR 0.95; 95% CI 0.69–1.32, respectively, but diabetes was higher compared to normoglycaemia (unadjusted HR 1.64; 95% CI 1.04–2.60; adjusted HR 1.57; 95% CI 0.98–2.51). In the time-varying model, there was no difference between IFG in either the unadjusted or adjusted models, for both any fracture and MOF ($p>0.05$). For diabetes, there was a significant difference between normoglycaemia in the adjusted model for any fracture ($p=0.046$), but not for MOF ($p=0.103$). An increased risk of fracture for women with diabetes was observed after accounting for time-varying risk factors. There was no difference in fracture risk detected for women with IFG.

**Keywords** Fracture · Major osteoporotic fracture · Diabetes mellitus · Impaired fasting glucose · Dysglycaemia

## Introduction

Impaired fasting glucose (IFG), an intermediate stage between normoglycaemia and diabetes, is increasing in prevalence [1]. We have recently reported that IFG affects approximately one-third of Australian women aged 20 years and older [2]. IFG is characterised by an elevated fasting plasma glucose (FPG) and it is defined by the American Diabetes Association (ADA) as a FPG level between 5.5 and 6.9 mmol/L (100–125 mg/dL) without antihyperglycaemic medication, whereas diabetes is classified by FPG ≥ 7.0 mmol/L (126 mg/dL) [3]. Diabetes is an epidemic disease that affects 415 million adults worldwide [4] and over 1.7 million people in Australia [5], with the prevalence

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of diabetes likely to increase [4, 6]. It can lead to serious health complications such as nephropathy [7], premature cardiovascular disease [8], retinopathy [9], peripheral neuropathy [10, 11], cognitive dysfunction [12], hypoglycaemia [13], lower limb amputation [14] and early mortality [15–17]. Women with diabetes have a higher fracture risk and sustain fractures at higher or normal bone mineral density (BMD) [11, 18–25]. By contrast, individuals with IFG do not appear to have different BMD or fracture risk compared to normoglycaemia [26, 27]. The biological mechanisms of IFG, diabetes and fractures have not been thoroughly explored. This longitudinal study aimed to determine whether there is any association between glycaemia status (normoglycaemia, IFG and diabetes) and risk of fractures in Australian women.

## Methods

### Study Design and Subjects

This study uses data from the Geelong Osteoporosis Study (GOS), a population-based study including participants residing in the Barwon Statistical Division (BSD). This region is situated in south-eastern Australia and has a stable population of approximately 280,000 and is largely representative of the Australian population, making it ideal for epidemiological research. The region also contains residents with a range of cultural and socio-economic characteristics. A complete description of the methodology has been published elsewhere [28]. At baseline, 1993–1997, an age-stratified sample of women aged 20 + years was selected at random from Commonwealth electoral rolls with a participation of 77%. For this analysis, we included women aged 50 + years ($n = 839$). Two hundred and sixty-four women were excluded because of the indeterminate glycaemia status or insufficient information. Thus, 575 women were eligible for baseline analysis. Those who were excluded were older and had lower weight, shorter height, lower lean mass, greater waist circumference, higher systolic and diastolic blood pressure, higher serum triglycerides, lower serum HDL cholesterol, with a lower proportion of smokers and lower mobility. Women were followed for a median period of 13.7 years (IQR 7.4–14.8) from their baseline appointment to date of first fracture, death or 31 December 2010, whichever occurred first.

Post-baseline fractures were ascertained using a computerised keyword search of radiological reports from all medical imaging centres serving the BSD region. Only clearly defined fractures were included, reports describing "suggestive" or "possible" fractures were excluded, except where there was a subsequent radiological report available to confirm the fracture. This method of fracture ascertainment has been previously validated [29] and utilised in epidemiological research [30]. Fractures were grouped as any fractures (all sites except fingers, toes and skull/face) and as major osteoporotic fractures (MOF; clinical spine, hip, proximal humerus and forearm). Pathological fractures and fractures resulting from high trauma (e.g. car accident) were excluded.

The study was approved by the Barwon Health Human Research Ethics Committee, and written informed consent was obtained from all participants.

### Measurements

All exposure measurements were performed at baseline. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, and body mass index (BMI) calculated as weight/height$^2$ (kg/m$^2$). Participants were categorised as obese if BMI ≥ 30.0 kg/m$^2$ [31]. Waist circumference (minimal abdominal, between ribs and iliac crest) and hip circumference (maximal gluteal) were measured to the nearest 0.5 cm. Whole body scans for all participants were performed using a dual-energy X-ray absorptiometry (DXA; Lunar DPX-L; Lunar, Madison, WI). These scans provided estimates of BMD (g/cm$^2$), body fat mass (kg), percentage body fat (%BF) and 'lean' mass (kg), which includes muscle, skin, connective tissue and the lean component of adipose tissue (water and protein). Both hips were also measured using DXA and the mean value for both the left and right femoral neck BMD was used in the analyses. The coefficient of variation for repeated scans was 1.6%. We used a cut point of %BF > 30 for obesity [32]. Blood pressure was measured in a sitting position using an automated device (Takeda Medical UA-751). Women were considered to be hypertensive if they had a systolic blood pressure over 140 mmHg and/or a diastolic pressure above 90 mmHg and/or use of antihypertensive medication. Physical activity, alcohol consumption, current smoking and medication use were self-reported by questionnaire. Women who reported undertaking regular physical activity were described as active, otherwise they were classified as inactive; high alcohol consumption was recognised if alcohol was consumed at least several times a week.

Venous blood was collected at baseline after an overnight fast. Fasting glucose was measured using an adaptation of the hexokinase-glucose-6-phosphate dehydrogenase method [33]. Blood samples were collected in sodium fluoride tubes by the major pathology centre in the region and glucose measurement was completed soon after blood collection. There was no long-term storage of blood samples before measurements. Diabetes was classified if FPG ≥ 7.0 mmol/L (126 mg/dL), self-reported diabetes and/or use of antihyperglycaemic agents (antihyperglycaemic medication use referred to medications taken regularly at baseline). IFG was considered present if FPG level was between 5.5 and

6.9 mmol/L (100–125 mg/dL), according to the 2003 ADA diagnostic criteria [3]. Commercially available kits and clinical chemistry analyser (Thermo Fisher Scientific) were used to determine total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides. The use of lipid lowering medications was investigated, but few women used these agents ($n = 51$). For these women, serum lipid results were still outside the range recommended by the World Health Organization (triglyceride < 2.0 mmol/L; HDL level > 1.29 mmol/L; LDL level ≤ 3.5 mmol/L [34]). Fasting blood samples were also analysed for serum C-terminal telopeptide (CTx) and procollagen type 1 N-terminal propeptide (P1NP), which represent bone turnover. Participants were asked to self-report the number of falls they experienced over the previous 12 months. The definition of a fall was "when you suddenly find yourself on the ground, without intending to get there, after you were in either a lying, sitting or standing position". For this analysis, participants were classified as fallers if they had fallen to the ground at least once during the previous 12 months. The Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD), an indicator of socio-economic status, was also determined. IRSAD accounts for high and low area-based income and occupation types including unskilled employment to professional positions, among other variables. A low score as measured by the IRSAD represents a more disadvantaged area and a high score a more advantaged area [35].

Additionally, the following measurements were collected in the same way at the 10-year follow-up visit (2004–2008): weight, height, BMI, waist and hip circumferences, DXA whole body and hip scans, blood pressure, fasting plasma glucose, smoking status, alcohol consumption, physical activity, medication use, falls and socio-economic status.

### Statistical Analyses

Participants' characteristics were summarised by frequencies (%) or mean (SD) or median (IQR) based on their glycaemia status (normoglycaemia, IFG and diabetes). One-way ANOVA or Kruskal–Wallis test was used to compare continuous data between the three glycaemia groups and categorical data were compared using the Chi-square test (or Fisher's exact test). Post hoc pairwise comparisons using Tukey, Dunn for continuous data and Chi-square for categorical data were also performed. Time to event was defined as time (years) from baseline to first fracture (event of interest), death or 31 December 2010, whichever occurred first (censored observation). Kaplan–Meier estimator of the survival function using product limit estimator was used for illustrating time to first fracture (survival) curves. The Log-rank test was used for bivariate comparison of time to event outcomes (e.g. comparing unadjusted risk of fracture) and Cox proportional hazards regression was implemented for multivariable survival analysis. Normoglycaemia was set as the reference category. Hazard ratios (HRs) and 95% confidence intervals (CIs) derived from the Cox model were reported. An extension of the Cox proportional hazards model with time-varying covariates was also performed to assess the effect of changes in variables at the 10-year follow-up visit [36]. The following variables were updated at the 10-year follow-up visit: diabetes status, age, weight, height, waist/hip circumference, blood pressure, fat mass, lean mass, smoking status, alcohol consumption, mobility, femoral neck BMD, cardiovascular medication use, glucocorticoid use and falls over the previous 12 months. Only age and femoral neck BMD were significant in the final multivariable model and thus all models were adjusted for these two variables.

For descriptive characteristics and the multivariable survival analysis, a $p$ value < 0.05 was considered statistically significant. For pairwise comparisons, a $p$ value of < 0.01 was considered significant. SPSS 22 and stata 15 were used for data analysis.

## Results

### Baseline and 10-year Follow-Up Data

Among 575 women, there were 256 (44.5%) with normoglycaemia, 250 (43.5%) with IFG and 69 (12.0%) with diabetes. There were 69 (27.0%) fractures in the normoglycaemia group, 71 (28.4%) in the IFG group and 22 (31.9%) in the diabetes group.

The descriptive statistics for these women at baseline are shown in Table 1. Age, BMI, FPG and triglycerides all increased with increasing dysglycaemia, as did the proportions of women with high blood pressure and low physical activity. Mortality was higher in women with diabetes during the study period. Women with diabetes also had lower bone formation as measured by serum P1NP and experienced more falls. However, BMD did not differ between the groups. For women with diabetes, 40.6% were taking antihyperglycaemic medications; most were taking either metformin (18.8%) or a sulfonylurea (29.0%). Few were using insulin (5.8%) and none were taking thiazolidinediones. Other variables were similar between the three groups. Following post hoc tests, compared to normoglycaemia, women with IFG were had a greater waist circumference and higher systolic blood pressure. Compared to diabetes, women with IFG were taller, had lower BMI, were less likely to be obese, had lower waist circumference, had lower triglyceride levels, higher HDL cholesterol levels, consumed more alcohol, were less likely to be physically inactive, had higher P1NP levels and were less likely to experience mortality over the study period.

**Table 1** Baseline descriptive characteristics of women at baseline stratified by glycaemic status (normoglycaemia, impaired fasting glucose (IFG) and diabetes)

| Variables | Normoglycaemia $n=256$ | IFG $n=250$ | Diabetes $n=69$ | $p$ value (ANOVA) | Normoglycaemia vs IFG | Normoglycaemia vs diabetes | IFG vs diabetes |
|---|---|---|---|---|---|---|---|
| Age (year) | 63.2 (56.2–72.1) | 66.6 (58.4–73.4) | 68.0 (62.1–88.1) | **0.004** | 0.033 | **<0.001** | 0.024 |
| Weight (kg) | 66.9 ± 12.6 | 69.8 ± 13.0 | 73.2 ± 17.6 | **<0.001** | 0.041 | **0.002** | 0.157 |
| Height (cm) | 159.5 ± 6.1 | 159.2 ± 6.3 | 156.6 ± 6.2 | **0.002** | 0.845 | **0.001** | **0.005** |
| BMI (kg/m$^2$) | 26.3 ± 4.6 | 27.5 ± 4.8 | 29.9 ± 7.2 | **<0.001** | 0.017 | **<0.001** | **0.002** |
| Obesity (%) | 48 (18.8) | 70 (28.0) | 32 (46.4) | **<0.001** | 0.014 | **<0.001** | **0.004** |
| Waist (cm) | 85.2 ± 10.7 | 88.5 ± 11.8 | 95.4 ± 11.9 | **<0.001** | **0.003** | **<0.001** | **<0.001** |
| Hip (cm) | 104.8 ± 10.3 | 107.0 ± 10.9 | 108.9 ± 13.1 | **0.009** | 0.058 | 0.019 | 0.433 |
| Body fat mass (kg) | 26.4 ± 9.2 | 28.6 ± 9.1 | 29.6 ± 10.5 | **0.006** | 0.016 | 0.033 | 0.747 |
| Lean mass (kg) | 37.5 ± 4.3 | 37.8 ± 4.7 | 38.7 ± 4.2 | 0.13 | 0.654 | 0.112 | 0.325 |
| Body fat % | 0.39 ± 0.08 | 0.41 ± 0.07 | 0.41 ± 0.08 | **0.01** | **0.011** | 0.144 | 1.000 |
| Femoral neck BMD (g/cm$^2$) | 0.845 ± 0.148 | 0.858 ± 0.152 | 0.864 ± 0.162 | 0.53 | 0.620 | 0.632 | 0.951 |
| Fasting plasma glucose (mmol/L) | 5.1 (4.9–5.3) | 5.7 (5.6–6.0) | 8.6 (6.8–11.6) | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Serum triglycerides cholesterol (mmol/L) | 1.4 ± 0.82 | 1.5 ± 0.73 | 2.2 ± 1.19 | **<0.001** | 0.368 | **<0.001** | **<0.001** |
| Serum HDL cholesterol (mmol/L) | 1.3 ± 0.40 | 1.3 ± 0.43 | 1.1 ± 0.35 | **<0.001** | 0.999 | **<0.001** | **<0.001** |
| Serum LDL cholesterol (mmol/L) | 3.2 ± 0.84 | 3.4 ± 0.92 | 3.1 ± 1.09 | **0.02** | 0.091 | 0.528 | 0.043 |
| Systolic blood pressure (mmHg) | 131.3 ± 23.5 | 137.4 ± 22.7 | 144.4 ± 22.0 | **<0.001** | **0.008** | **<0.001** | 0.076 |
| Diastolic blood pressure (mmHg) | 78.9 ± 12.1 | 80.5 ± 12.8 | 83.9 ± 16.8 | **0.02** | 0.353 | 0.015 | 0.141 |
| Hypertension (y/n) (%)* | 93 (36.9) | 111 (45.3) | 41 (63.1) | **<0.001** | 0.057 | **<0.001** | 0.011 |
| Current smoker (%) | 23 (9.0) | 25 (10.0) | 10 (14.5) | 0.4 | 0.697 | 0.179 | 0.290 |
| High alcohol consumption (%)[a] | 50 (19.5) | 71 (28.4) | 6 (8.7) | **<0.001** | 0.019 | 0.034 | **0.001** |
| Low physical activity (%) | 88 (34.4) | 97 (38.8) | 45 (65.2) | **<0.001** | 0.301 | **<0.001** | **<0.001** |
| Antihyperglycaemic medication use (%) | 0 (0) | 0 (0) | 28 (40.6) | – | – | – | – |
| Insulin | 0 (0) | 0 (0) | 4 (5.8) | – | – | – | – |
| Metformin | 0 (0) | 0 (0) | 13 (18.8) | – | – | – | – |
| Sulfonylurea | 0 (0) | 0 (0) | 20 (29.0) | – | – | – | – |
| Thiazolidinediones | 0 (0) | 0 (0) | 0 (0) | – | – | – | – |
| ln(CTx) (ng/L)[b] | 5.82 ± 0.80 | 5.85 ± 0.76 | 5.63 ± 0.68 | 0.114 | 0.922 | 0.164 | 0.098 |
| ln(P1NP) (µg/L)[c] | 3.61 ± 0.55 | 3.64 ± 0.49 | 3.36 ± 0.52 | **0.002** | 0.808 | **0.005** | **0.001** |
| Falls (y/n) | 37 (14.5) | 51 (20.4) | 22 (31.9) | **0.004** | 0.081 | **0.001** | 0.044 |
| IRSAD | | | | 0.310 | 0.114 | 0.636 | 0.728 |
| Quintile 1 (%) | 42 (16.4) | 56 (22.4) | 12 (17.4) | | | | |
| Quintile 2 (%) | 51 (19.9) | 57 (22.8) | 14 (20.3) | | | | |
| Quintile 3 (%) | 59 (23.0) | 58 (23.2) | 21 (30.4) | | | | |
| Quintile 4 (%) | 41 (16.1) | 39 (15.6) | 10 (14.5) | | | | |
| Quintile 5 (%) | 63 (24.6) | 40 (16.0) | 12 (17.4) | | | | |
| Mortality (y/n) | 44 (17.2) | 51 (20.4) | 27 (39.1) | **<0.001** | 0.250 | **<0.001** | **<0.001** |

**Table 1** (continued)

Bold values indicate a significant difference between groups

Data are shown as median (interquartile range) or mean (±) or *n* (%)

Please note that some women were taking multiple different types of antihyperglycaemic medication

For pairwise comparisons, a *p* value of $<0.01$ was considered significant

*Missing data: hypertension $n=5$, CTx, $n=12$, P1NP $n=73$, falls $n=1$

[a]Defined as ≥ 3 standard drinks per day

[b]C-terminal telopeptide

[c]Procollagen type 1 N-terminal propeptide

Descriptive statistics for women at the 10-year follow-up are presented in Table 2. Women with IFG and diabetes had higher weight and BMI, were more likely to be obese, had greater waist and hip circumferences, higher body fat, lean mass and proportion of body fat. Femoral neck BMD was also higher in women with IFG and diabetes, as well as blood pressure and proportion with hypertension. Women with diabetes were also more likely to have low physical activity. There were no differences in any of the other variables. Post hoc tests showed that, compared to normoglycaemia, women with IFG were heavier, had higher measures of adiposity (BMI, obesity, waist/hip circumferences, body fat mass). There were no differences detected at a $p<0.01$ level between women with IFG and diabetes.

### Fracture and Glycaemia Status

During a median follow-up of 13.7 years (6433 person-years), 162 women sustained a fracture at any site and 104 sustained a MOF (Table 3). Figure 1a, b shows the Kaplan–Meier plots for any fracture and MOF, respectively. The unadjusted risk of fracture was higher in diabetes (HR 1.64; 95% CI 1.02–2.63, $p=0.04$), however, IFG and normoglycaemia had similar risk (HR 1.06; 95% CI 0.76–1.47, $p=0.75$). In a model adjusted for age and femoral neck BMD, the risk for a fracture at any site was higher for women with diabetes compared to normoglycaemia (HR 1.59; 95% CI 0.98–2.58, $p=0.06$). IFG had a similar risk to the normoglycaemia group (HR 1.01; 95% CI 0.72–1.41, $p=0.95$).

The results for MOFs were similar to that for any fracture. In the unadjusted model, the fracture risk for women with IFG was similar to that for normoglycaemia (HR 1.02; 95% CI 0.74–1.40, $p=0.92$). Diabetes had a higher risk of MOF compared to normoglycaemia (unadjusted HR 1.64; 95% CI 1.04–2.60, $p=0.04$). For the model adjusted for age and femoral neck BMD (Fig. 1b), again IFG did not appear to have an increased risk of MOF (HR 0.95; 95% CI 0.69–1.32, $p=0.77$) compared to normoglycaemia; however, diabetes was associated with a trend of increased risk for MOF (HR 1.57; 95% CI 0.98–2.51, $p=0.06$).

Further adjustment for other variables (lean and fat mass, mobility, hypertension, falls and bone turnover markers) did not affect the reported associations (Fig. 2).

### Time-Varying Data

The model adjusted for changes in variables at 10-year follow-up is shown in Table 3. For any fracture, there was no difference between normoglycaemia and IFG in either unadjusted (HR 1.08; 95% CI 0.77–1.52, $p=0.652$) or age and femoral neck BMD-adjusted (1.09; 95% CI 0.77–1.53, $p=0.627$) models. For diabetes, there was a trend observed for the unadjusted model (1.57; 95% CI 0.99–2.47, $p=0.053$). However, any fracture risk was higher for women with diabetes in the age and femoral neck BMD-adjusted model (1.60; 95% CI 1.01–2.55, $p=0.046$).

For MOFs, there were no differences observed between IFG and normoglycaemia in either the unadjusted (1.22; 95% CI 0.79–1.88, $p=0.369$) or age and femoral neck BMD-adjusted models (1.20; 95% CI 0.77–1.85, $p=0.420$). No differences were observed in unadjusted (1.71; 95% CI 0.96–3.04, $p=0.069$) or age and femoral neck BMD-adjusted (1.63; 95% CI 0.91–2.92, $p=0.103$) models for diabetes.

Further adjustment for other variables did not affect the reported associations.

## Discussion

This longitudinal study investigated the association between IFG and diabetes and risk of fractures over a median follow-up of 13.7 years in Australian women. Individuals with diabetes were older, heavier and had higher serum triglycerides, blood pressure and lower physical inactivity compared to the IFG and normoglycaemia groups. The diabetes group also had lower serum HDL cholesterol compared with the other groups. In the unadjusted models, fracture risk (any and MOF) was higher in diabetes compared to normoglycaemia; however, IFG and normoglycaemia had apparently similar

**Table 2** 10-year follow-up descriptive characteristics of women at baseline stratified by glycaemic status (normoglycaemia, impaired fasting glucose (IFG) and diabetes)

| Variables | Normoglycaemia $n=190$ | IFG $n=73$ | Diabetes $n=44$ | $p$ value (ANOVA) | Normoglycaemia vs IFG | Normoglycaemia vs diabetes | IFG vs diabetes |
|---|---|---|---|---|---|---|---|
| Age (year) | 70.1 (63.7–77.1) | 70.6 (64.6–75.9) | 71.9 (65.1–76.6) | 0.700 | 0.479 | 0.203 | 0.245 |
| Weight (kg) | 67.9 ± 11.6 | 73.6 ± 12.5 | 76.3 ± 14.2 | **< 0.001** | **0.002** | **< 0.001** | 0.481 |
| Height (cm) | 159.0 ± 6.3 | 158.6 ± 6.0 | 158.7 ± 7.0 | 0.904 | 0.907 | 0.965 | 0.996 |
| BMI (kg/m$^2$) | 26.8 ± 4.3 | 29.3 ± 5.0 | 30.5 ± 6.4 | **< 0.001** | **0.001** | **< 0.001** | 0.408 |
| Obesity (%) | 41 (21.6) | 30 (41.1) | 23 (52.3) | **< 0.001** | **0.001** | **< 0.001** | 0.239 |
| Waist (cm)* | 88.6 ± 11.7 | 94.2 ± 12.3 | 97.7 ± 13.3 | **< 0.001** | **0.002** | **< 0.001** | 0.290 |
| Hip (cm)* | 103.4 ± 10.0 | 107.2 ± 10.9 | 109.1 ± 11.9 | **0.001** | 0.028 | **0.004** | 0.602 |
| Body fat mass (kg)* | 27.1 ± 8.9 | 31.0 ± 9.3 | 30.9 ± 9.0 | **0.002** | **0.004** | 0.036 | 0.998 |
| Lean mass (kg)* | 37.1 ± 3.6 | 38.5 ± 3.8 | 39.5 ± 5.0 | **< 0.001** | 0.025 | **0.001** | 0.430 |
| Body fat % | 0.38 ± 0.09 | 0.41 ± 0.06 | 0.38 ± 0.12 | **0.022** | 0.020 | 0.986 | 0.097 |
| Femoral neck BMD (g/cm$^2$)* | 0.810 ± 0.131 | 0.851 ± 0.135 | 0.896 ± 0.150 | **< 0.001** | 0.071 | **0.001** | 0.193 |
| Fasting plasma glucose (mmol/L) | 4.9 (4.7–5.2) | 5.7 (5.5–6.0) | 7.6 (6.2–8.9) | **< 0.001** | **< 0.001** | **< 0.001** | 0.060 |
| Systolic blood pressure (mmHg)* | 132.6 ± 18.9 | 137.8 ± 17.2 | 139.1 ± 16.6 | **0.035** | 0.113 | 0.093 | 0.927 |
| Diastolic blood pressure (mmHg)* | 77.0 ± 10.5 | 80.0 ± 10.2 | 74.5 ± 10.2 | **0.022** | 0.111 | 0.325 | 0.019 |
| Hypertension (y/n) (%) | 119 (62.6) | 55 (75.3) | 38 (86.4) | **0.004** | 0.051 | **0.003** | 0.153 |
| Current smoker (%) | 13 (6.8) | 6 (8.2) | 3 (6.8) | 0.923 | 0.699 | 0.995 | 0.783 |
| High alcohol consumption[a] (%)* | 10 (5.4) | 1 (1.4) | 0 (0.0) | 0.125 | 0.152 | 0.130 | 1.000 |
| Low physical activity (%) | 58 (30.5) | 21 (28.8) | 23 (52.3) | **0.014** | 0.780 | **0.006** | 0.011 |
| Antihyperglycaemic medication use (%) | 0 (0) | 0 (0) | 22 (50.0) | – | – | – | – |
| Insulin | 0 (0) | 0 (0) | 4 (9.1) | – | – | – | – |
| Metformin | 0 (0) | 0 (0) | 20 (45.5) | – | – | – | – |
| Sulfonylurea | 0 (0) | 0 (0) | 0 (0.0) | – | – | – | – |
| Thiazolidinediones | 0 (0) | 0 (0) | 0 (0.0) | – | – | – | – |
| Falls (y/n) | 1 (0.5) | 0 (0.0) | 0 (0.0) | – | – | – | – |
| IRSAD | | | | 0.369 | 0.183 | 0.743 | 0.253 |
| Quintile 1 (%) | 31 (16.3) | 18 (24.7) | 9 (20.5) | | | | |
| Quintile 2 (%) | 38 (20.0) | 15 (20.6) | 10 (22.7) | | | | |
| Quintile 3 (%) | 38 (20.0) | 10 (13.7) | 10 (22.7) | | | | |
| Quintile 4 (%) | 46 (24.2) | 11 (15.1) | 10 (22.7) | | | | |
| Quintile 5 (%) | 37 (19.5) | 19 (26.0) | 5 (11.4) | | | | |
| Mortality (y/n) | 18 (9.5) | 9 (12.3) | 7 (15.9) | 0.437 | 0.495 | 0.213 | 0.585 |

Bold values indicate a significant difference between groups

Data are shown as median (interquartile range) or mean (±) or $n$ (%)

Please note that some women were taking multiple different types of antihyperglycaemic medication

For pairwise comparisons, a $p$ value of $<0.01$ was considered significant

*Missing data: Waist/hip circumference $n=4$, Fat/Lean mass $n=8$, Femoral neck BMD $n=12$, Blood Pressure $n=16$, Alcohol consumption $n=6$

[a]Defined as ≥ 3 standard drinks per day

**Table 3** Unadjusted and model adjusted associations between fracture and glycaemia status (normoglycaemia, impaired fasting glucose (IFG) and diabetes) for all fractures (except fingers, toes and skull/face) and major osteoporotic fractures (MOF; spine, hip, proximal humerus and wrist)

| | Normoglycaemia $n=256$ | IFG $n=250$ | $p$ value | Diabetes $n=69$ | $p$ value |
|---|---|---|---|---|---|
| Baseline covariates | | | | | |
| Any fracture ($n=162$) | | | | | |
| Unadjusted | Ref | 1.06 (0.76–1.47) | 0.75 | 1.64 (1.02–2.63) | 0.04 |
| Adjusted* | Ref | 1.01 (0.72–1.41) | 0.95 | 1.59 (0.98–2.58) | 0.06 |
| MOF fracture ($n=104$) | | | | | |
| Unadjusted | Ref | 1.02 (0.74–1.40) | 0.92 | 1.64 (1.04–2.60) | 0.04 |
| Adjusted* | Ref | 0.96 (0.69–1.3) | 0.77 | 1.57 (0.98–2.51) | 0.06 |
| Time-varying covariates | | | | | |
| Any fracture ($n=162$) | | | | | |
| Unadjusted | Ref | 1.08 (0.77–1.52) | 0.652 | 1.57 (0.99–2.47) | 0.053 |
| Adjusted* | Ref | 1.09 (0.77–1.53) | 0.627 | 1.60 (1.01–2.55) | 0.046 |
| MOF fracture ($n=104$) | | | | | |
| Unadjusted | Ref | 1.22 (0.79–1.88) | 0.369 | 1.71 (0.96–3.04) | 0.069 |
| Adjusted* | Ref | 1.20 (0.77–1.85) | 0.420 | 1.63 (0.91–2.92) | 0.103 |

Data presented as hazard ratios (HR) and 95% CIs

*MOF* major osteoporotic fracture, *IFG* impaired fasting glucose

*Adjusted for age and femoral neck BMD. No other confounders were statistically significant

risk. There were no differences detected after adjustment for age and femoral neck BMD for either IFG or diabetes. In the time-varying models, no differences were observed between IFG and normoglycaemia; however, women with diabetes had a higher risk of any fracture in the adjusted models.

Our data are consistent with other studies, which have reported that type 2 diabetes increases the risk of fractures [11, 18–25]. A large longitudinal study in Norway [37] has shown that women with type 2 diabetes had nearly twofold increased risk of hip fracture compared to those without diabetes. In addition, the relative risk (RR) did not change when women with insulin treatment were excluded from the analysis (RR 1.8, 95% CI, 1.1–3.0). In an American prospective cohort study, Schwartz et al. [11] reported that women with diabetes (non-insulin dependent) had an increased risk for fractures of the hip (RR 1.82; 95% CI, 1.24–2.69) and proximal humerus (RR 1.94, 95% CI, 1.24–3.02) compared those with normal fasting glucose level. Another American cohort study with older adults [26] has demonstrated that diabetes mellitus was associated with increased fracture risk (RR 1.64, 95% CI, 1.07–2.51). Vestergaard [38] and Janghorbani et al. [39] have also shown in meta-analyses that women with type 2 diabetes had higher fracture risk compared to controls (RR 1.38, 95% CI, 1.25–1.53 and RR 2.8, 95% CI, 1.2–6.6, respectively).

The effect of IFG on risk of fracture is still unclear and few studies have been conducted. One study conducted in another Australian cohort [27] including 3477 women aged ≥ 40 years, followed for 5 years, showed in unadjusted and adjusted models that FPG was not associated with an increase in the incidence of fractures. However, this study did report a 25–30% reduction in fracture risk for those with prediabetes (defined as IFG or impaired glucose tolerance). This is different to what we reported in this study, and may be due to differences in the studies. While this study used radiologically confirmed fractures, the Gagnon et al. study used self-reported fractures. The follow-up time was also different (13 vs. 5 years) as well as the definition of IFG; we used the ADA criteria ($5.5 \leq \text{FPG} < 7.0$ mmol/L), while the other study used the WHO criteria ($6.1 \leq \text{FPG} < 7.0$ mmol/L). Another study has also reported a reduction in fracture risk for women with elevated 2-h glucose levels [40]; however, there was no association detected when considering FPG, which is consistent with our study. Our results are also similar to several other studies that used radiologically ascertained fractures [26, 41], which report no differences in fracture risk between IFG and normoglycaemia.

The pathophysiological mechanisms involving fracture in type 2 diabetes are still unclear. Some possible reasons include the direct effect of hyperglycaemia on bone, that have been detailed in several reviews [42–44] and include glycosuria that may cause hypercalciuria, accumulation of advanced glycation end products (AGEs) in the collagen fibres which may impair bone structure, a decrease of insulin like growth factors-I (IFG-I) and plasma insulin levels due to its regulation of bone cell metabolism. Another reason may be the lower level of osteocalcin in individuals with type 2 diabetes. This hormone, which is secreted by osteoblasts, plays a role in bone formation and glucose homeostasis [45]. Other possible reasons for the increased fracture risk in individuals with diabetes include lower bone turnover and an increased risk of falls [46]. In this study, we investigated

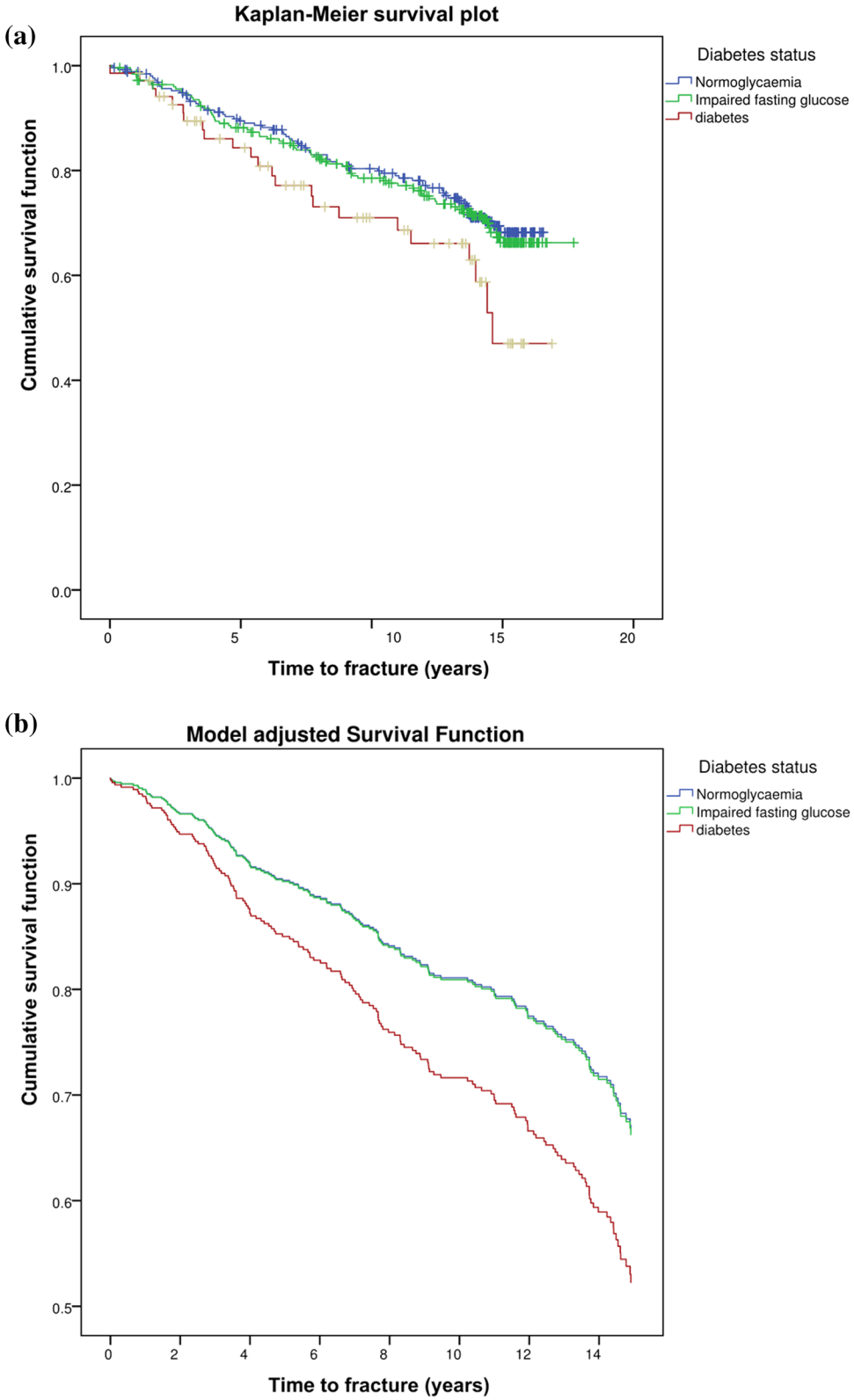


**Fig. 1** Unadjusted (**a**) and adjusted (**b**), cumulative survival functions using baseline data for diabetes status versus any-fracture survival time, years (x-axis). Adjusted model includes age at cohort entry and bone mineral density

bone turnover markers and falls as potential confounding variables in the models, but neither was an independent predictor of fracture risk nor attenuated the observed associations. In a cross-sectional study, we have also previously reported no differences in trabecular bone score (TBS) or TBS-adjusted FRAX score for women with IFG compared to those with normoglycaemia [47].

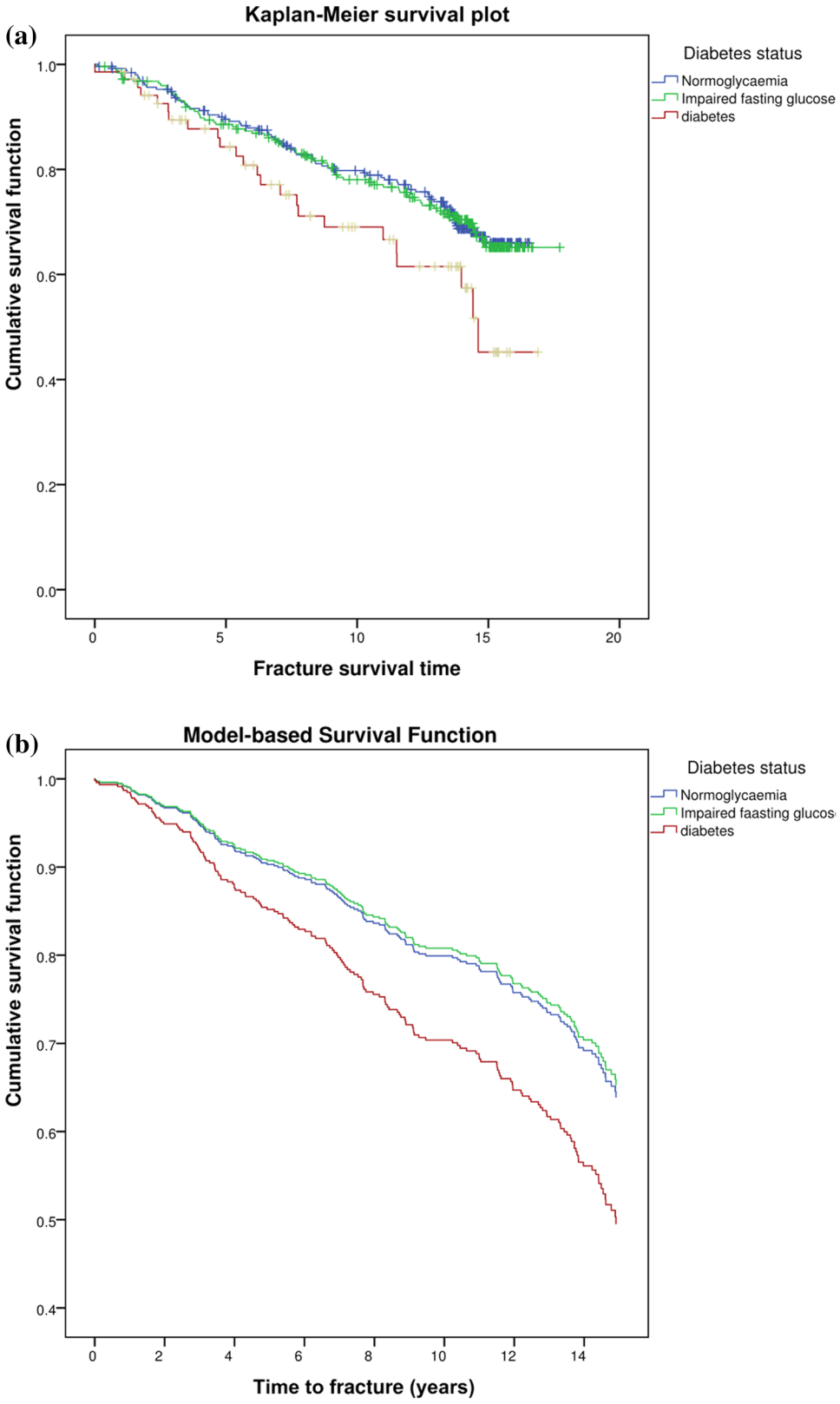


**Fig. 2** Unadjusted (**a**) and adjusted (**b**), cumulative survival functions using baseline data for diabetes status versus fragility fracture survival time, years (x-axis). Adjusted model includes age at cohort entry and bone mineral density

We recognise that this study has some strengths and limitations. One strength is that participants were representative of the general population, as they were randomly selected from electoral rolls. Since we used radiologically confirmed fractures as the endpoint of this study, we minimised bias related to loss of follow-up, as we could confirm

their incident fractures independently. We also obtained data on date of death from the Australian Institute for Health and Welfare, which allowed us to confirm death dates, even if the participants had dropped out of the study. We had a long follow-up period of a median 13.7 years, and we confirmed changes in diabetes status at the 10-year follow-up visit during this time period. However, we may not have had sufficient statistical power in this study to detect differences between the glycaemia groups, although the increase in risk we observed for IFG compared to normoglycaemia (unadjusted: 1.22, adjusted: 1.20) was similar to that observed in a recent study of patients with insulin-treated type 2 diabetes [48]. Our study also used a detailed method of diabetes ascertainment, including self-report, medication use and FPG measurement. However, we were unable to distinguish type 1 from type 2 diabetes, and fracture risk may have been different between these two groups. We also were unable to determine the duration of diabetes, which may have impacted the reported results. This study included women only, and the majority was white, therefore these results may not be generalisable to other populations. Participants who were excluded from this study due to a lack of information to determine diabetes status were different to women included in the study. Lastly, some of our data were self-reported; however, most analyses were based on objective measures and radiologically confirmed fracture reports.

## Conclusions

An increased risk of fracture for women with diabetes was observed in time-varying models. There was no difference in fracture risk detected for women with IFG.

**Acknowledgements** The authors would like to acknowledge Dr Adrienne O'Neil for her role in obtaining the lipid levels in sera, Associate Professor Paul Lewandanski and his laboratory for performing the lipid analyses and the Australian Institute for Health and Welfare (AIHW) for death data. The Geelong Osteoporosis Study was supported by the Victorian Health Promotion Foundation, National Health and Medical Research Council (NHMRC), Australia (Projects 251638 and 628582), the Geelong Regional Medical Foundation; however, the funding bodies played no part in either the design or conduct of the study, the collection, management, analysis and interpretation of the data or the preparation or review of the paper. LFFA and MAS are supported by Postgraduate Scholarships from Deakin University. KLH-K is supported by an Alfred Deakin Postdoctoral Research Fellowship.

### Compliance with Ethical Standards

**Conflict of interest** LLFA, KLH-K, MM, MAS, MAK and JAP have no other conflict of interest to declare.

**Human and Animal Rights and Informed Consent** This study was ethically approved by the Human Research and Ethic Committees of Barwon Health (Geelong, Australia) and performed in accordance with the criteria defined by the rules of the committee.

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